

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 September 2004 (10.09.2004)

PCT

(10) International Publication Number
WO 2004/075896 A1

- (51) International Patent Classification⁷: **A61K 31/47, A61P 11/08**
- (21) International Application Number:
PCT/EP2004/001960
- (22) International Filing Date: 27 February 2004 (27.02.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
03004184.2 27 February 2003 (27.02.2003) EP
- (71) Applicant (for all designated States except US): **CHIESI FARMACEUTICI S.P.A.** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **RAZZETTI, Roberta** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). **PASTORE, Fiorella** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).
- (74) Agents: **BIANCHETTI, Giuseppe** et al.; Via Rossini, 8, I-20122 Milano (IT).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **MEDICAMENT COMPRISING A HIGHLY POTENT LONG-LASTING BETA2-AGONIST IN COMBINATION WITH OTHER ACTIVE INGREDIENTS**

(57) Abstract: The present invention relates to the use of a bronchodilator in combination with one or more further active ingredients for the treatment of respiratory disorders and especially asthma and chronic obstructive pulmonary disease (COPD), and to pharmaceutical compositions containing said active ingredients. In particular, the invention relates to the use of the long-acting β_2 -agonist 8-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl-2(1H)-quinolinone and/or physiologically acceptable salts and/or solvates thereof as a bronchodilator in combination with other active ingredients.



WO 2004/075896 A1

MEDICAMENT COMPRISING A HIGHLY POTENT LONG-LASTING BETA2-AGONIST IN
COMBINATION WITH OTHER ACTIVE INGREDIENTS

BACKGROUND OF THE INVENTION

Asthma is a disease which is becoming more prevalent and is the most common disease of childhood. It can be identified by recurrent wheeze and intermittent air flow limitation. Despite many advances in its understanding, said pathology remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the most important feature of asthma. Recently there has been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving irreversible narrowing of the airways and fibrosis of the lung tissue. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

The symptoms may be controlled by first generation β_2 -adrenoceptor agonists such as salbutamol, fenoterol and terbutalin or second generation ones such as formoterol and salmeterol (long-acting β_2 -agonists) which overcome the disadvantage of the short duration of action particularly for patients with nocturnal asthma. Prophylactic therapy, instead, is typically provided by corticosteroids such as beclometasone dipropionate, fluticasone propionate mometasone furoate and budesonide.

Another respiratory disease whose incidence is steadily increasing throughout the world is chronic obstructive pulmonary disease (COPD). Most patients with COPD have acquired their lung disease through smoking cigarettes. Depending upon trends in tobacco smoking, it is set to rise to fifth

most prevalent cause of disability, worldwide by 2020 (Leckie M et al *Exp Opin Invest Drugs* 2000, 9, 3-23).

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic
5 bronchitis or emphysema.

Chronic bronchitis is characterized by excessive secretion of bronchial mucus, whereas emphysema denotes abnormal, permanent enlargement of air spaces distal to the terminal bronchiole, with destruction of their walls and without obvious fibrosis (American Thoracic Society). Each condition is
10 treated as specific diseases.

Chronic obstructive bronchiolitis is due to obstruction of the peripheral airways as a result of inflammation in the bronchioles.

Drugs intended for the treatment of lung diseases such as asthma and COPD are currently administered by pulmonary delivery which relies on
15 inhalation of an aerosol through the mouth and throat so that the drug substance can reach the lung. They can be administered as aqueous or hydroalcoholic formulations through a nebuliser, as dry powders by means of Dry Powder Inhalers or in halogenated hydrocarbon propellants. The propellant-based systems require suitable pressurized metered-dose inhalers
20 (pMDIs) which release a metered dose of medicine upon each actuation.

Complicated therapy with different medications and devices may lead to poor compliance of the patients, so to under-treatment and, in turn, negative impact on their quality of life. This is dramatically evident in the case of long-term management of chronic asthma, in particular with prophylactic
25 treatments, such as inhaled steroids, which do not give immediate symptom relief. Recent therapeutic strategy is aimed at both controlling the symptoms and reducing the inflammation by fixed combinations of a long-acting β_2 -agonist and a corticosteroid.

Combinations containing salmeterol and fluticasone propionate, both under the form of dry powder and HFA formulations, are currently on the market under the trade name of Seretide®. Each dose of the combined formulations is administered twice-daily. Each inhalation from the powder
5 formulation can deliver a nominal dose of 50 microg of *rac*-salmeterol xinafoate and one of three doses of fluticasone propionate 100, 250 and 500 microg. Using the HFA formulation, each puff from the inhaler can deliver a nominal dose of 25 microg of salmeterol and 50, 125 or 250 microg of fluticasone.

10 A combination containing formoterol and budesonide in form of dry powder is currently on the market under the trade name of Symbicort® and each single dose is administered twice-daily. Each inhalation can deliver a nominal dose of 6 microg of *rac*-formoterol fumarate and either 100 or 200 microg of budesonide.

15 Several articles in the scientific literature deal with the use of β_2 -agonists in combination with other classes of drugs, in particular corticosteroids and anticholinergics.

Moreover, various kinds of combinations have been proposed in the patent literature.

20 Nevertheless, it has never been demonstrated in the prior art that, by using a long-acting β_2 -agonist (LABA) in the combination therapy, an increment both of the bronchodilating and of the anti-inflammatory efficacy can be achieved so as making possible to reduce the dose without affecting the therapeutic effect.

25 In this respect, for example, it would be highly advantageous to provide a combination of a β_2 -agonist and a steroid which: i) while keeping the rapid onset of action, has a longer duration of action in such a way as that the formulation can be administered once a day so delaying the possible

appearance of tolerance towards the β_2 -agonist and with a great improvement of the compliance of patients, in particular of those with chronic and nocturnal asthma; *ii*) allows to reduce the dose of corticosteroid.

2(1H)-quinolone derivatives have been disclosed in the past, for instance in EP 147719 and WO 00/75114, and characterized as potent long lasting bronchodilating agents useful for the treatment or prophylaxis of various chronic obstructive pulmonary disease.

A medicament comprising a particular 2(1H)-quinolinone derivative LABA and a corticosteroid for the treatment of inflammatory or obstructive airways diseases has been recently disclosed in WO 02/45703. In the description it is stated in general terms that it is possible to use said combination to reduce the dosages of corticosteroid required for a given therapeutic effect compared with those required using treatment with a corticosteroid alone, but no supporting evidence is reported.

8-Hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl] amino]ethyl]-2(1H)-quinolinone hydrochloride salt, known with the experimental code TA 2005 is a highly potent long-acting β_2 -agonist also characterized by a rapid onset of action, disclosed for the first time in EP 147719. In the description it is stated that the compound can be administered either orally or parenterally. As far as the daily dose is concerned, only a very broad generic range is reported, i.e. 0.01 to 30 μg , especially 0.01 to 3 μg per kg of body weight (corresponding to about 0.7 to 2100 μg , especially 0.7 to 210 μg). JP 09-309830 referred to its use as an anti-inflammatory agent by inhalation but even in this case, a broad generic range of doses was reported, i.e. from 1 to 20 μg , for example about 3 to 10 μg .

In Eur Resp J 8 (Suppl 19), 1995, 258s, the results of two clinical studies were shown. In the latter (P1300), mild asthmatics inhaled single doses of 6 and 9 μg TA 2005 and placebo from a metered dose nebuliser system at

one week intervals. At these two dose levels TA 2005 produced a rapid and long lasting bronchodilation. The former (P1301) concerned a randomised, double blind, placebo-controlled, rising dose, safety study. Single doses of either 0.8, 1.6, 3.2, 6.4, 9.6, 12.8 µg were inhaled by healthy male volunteers
5 from a metered dose nebuliser system. TA 2005 caused a dose-dependent increase in heart rate, tremor and pulmonary function and a decrease in plasma potassium. According to the authors, the maximum no adverse effect dose of TA 2005 was 9.6 µg. A very large therapeutic window between 0.8 and 9.6 µg has been therefore suggested, but an efficacious and safe dose has not been
10 identified.

In EP 1157689 the applicant described aerosol pharmaceutical compositions comprising a β_2 -agonist belonging to the class of phenylalkylamino derivatives in solution in a HFA propellant and a co-solvent whose apparent pH was adjusted to between 2.5 and 5.0 in order to guarantee
15 an adequate shelf-life of the medicament. In the description, it has been stated that TA 2005 formulations will be advantageously suitable for delivering 2-10 µg/dose, preferably 3-5 µg/dose. A 3.5 µg/dose HFA 134a formulation containing 12% w/w ethanol and 1.0% IPM has been reported in example 7.

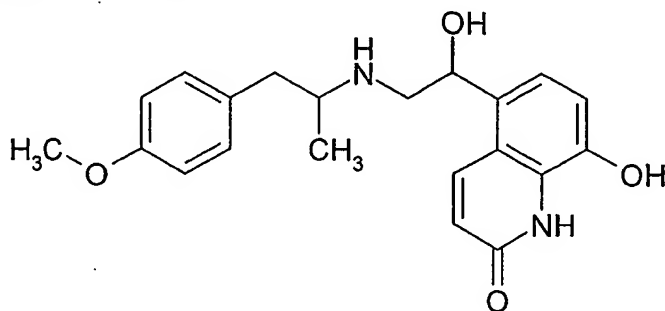
Several other patents or patent applications, i.e. US 6221398,
20 US 5874063, US 6030604, WO 98/41193, WO 98/31352 , WO 01/78693, WO 01/89480 and WO 03/080939 mention TA 2005 in a list of possible β_2 -agonists in compositions comprising other classes of drugs such as corticosteroids, anticholinergics or phosphodiesterase-4-inhibitors.

In none of the documents of the prior art, specific combination products of
25 TA 2005 with other active ingredients have been disclosed provided with such a beneficial pharmacological profile as the combination products of the invention.

OBJECT OF THE INVENTION

The present invention provides a medicament comprising, separately or

together: 8-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methyl ethyl]amino]ethyl]-2(1H)-quinolinone and/or a physiologically acceptable salt and/or solvate thereof (compound A), and one or more further active ingredients, wherein said further active ingredient is preferably selected
5 from a corticosteroid, an anticholinergic/antimuscarinic agent or a phosphodiesterase-4-inhibitor.



A

A corticosteroid useful for the treatment of the inflammatory or obstructive airways diseases can be preferably selected from the group of budesonide and its epimers, beclometasone dipropionate, flunisolide,
10 fluticasone propionate, ciclesonide, triamcinolone acetonide, rofleponide palmitate and mometasone furoate, for simultaneous, sequential or separate administration in the prophylaxis or treatment of an inflammatory or obstructive airways disease such as asthma or COPD.

An anticholinergic/antimuscarinic agent can be selected from
15 compounds available on the market such as ipratropium bromide, oxitropium bromide or tiotropium bromide or other selective antimuscarinic M3 agents.

Suitable antimuscarinic drugs are also glycopyrrolate or its 3R-2'R epimer.

The preferred phosphodiesterase-4-inhibitors are ciclomilast and
20 roflumilast.

In a further aspect, the present invention provides a pharmaceutical composition comprising, together, effective amounts of (A) as hereinbefore

defined and one or more further active substances, as hereinbefore defined, optionally together with at least one pharmaceutically acceptable carrier.

The invention further provides the use of (A) as hereinbefore defined in combination with one or more further active substances, as hereinbefore
5 defined in the preparation of a pharmaceutical composition or a kit for the prophylaxis or treatment, by simultaneous, sequential or separate administration of (A) and the other active substances, of any inflammatory or obstructive airways disease.

One of the preferred combination products comprises compound A as
10 hydrochloride salt (TA 2005, also known under the experimental code CHF 4226) and a corticosteroid. It has indeed been found that, upon combination of such β_2 -agonist and a corticosteroid, both the bronchodilator and the anti-inflammatory effects increase.

The current pharmacological therapies for COPD are aimed at relieving
15 symptoms and reducing exacerbations. Bronchodilators cause only a little improvement in spirometric measurements, but may improve symptoms and exercise tolerance and reduce the infective exacerbations.

In COPD patients, the contribute of anticholinergic/antimuscarinic drugs is important, because they relieve the airways constriction due to the
20 vagal cholinergic tone.

A combination product comprising a long-acting β_2 -adrenoceptor agonist such as TA 2005 and an antimuscarinic drug is a potential very interesting therapy for COPD. In the combination product of the invention a synergistic effect between TA 2005 and tiotropium bromide has been
25 demonstrated in terms of bronchospasm control both in vitro and in vivo animal models.

The efficacy of the combination can be enhanced by the addition of a corticosteroid that can act synergistically with TA 2005 on the inflammatory

mediators. In fact, as demonstrated in the examples that follow, TA 2005 gives rise to synergistic interaction in controlling plasma exudations in the airways.

In this respect, another useful combination includes a
5 phosphodiesterase-4-inhibitor, able to relax airway smooth muscle, to suppress the activation of specific inflammatory cells and to modulate the activity of pulmonary nerves.

Accordingly, it might be possible to reduce in the combination products of the invention, for any active ingredient, the dose recommended for each
10 component without affecting the therapeutic effect, so diminishing the risk of appearance of the side-effects associated to its use.

In a particular aspect, the present invention provides a medicament wherein the compound (A) is present in the combination as hydrochloride salt (TA 2005) in a suitable amount to provide a daily dose comprised between
15 0.5 and 8 μ g, advantageously between 1 and 6 μ g, preferably between 1 and 4 μ g, for simultaneous, sequential or separate administration once or twice daily, preferably once daily, in the treatment of an inflammatory or obstructive airways disease such as asthma or COPD.

Useful combination products contain TA 2005 and a corticosteroid
20 and/or an anticholinergic/antimuscarinic agent and/or a phosphodiesterase-4-inhibitor.

Preferred examples of combination products include:

- TA 2005 and an acetal corticosteroid selected from budesonide and ciclesonide;
- 25 - TA 2005 and tiotropium bromide as a selective M1 and M3 muscarinic receptors antagonist;
- TA 2005 + a corticosteroid + an antimuscarinic;
- TA 2005 + an antimuscarinic + a phosphodiesterase-4-inhibitor.

Effective doses of TA 2005 in the combination product can be 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 μ g.

It has indeed been found that at these dosage strengths TA 2005 is therapeutically effective upon inhalation.

5 The bronchodilator efficacy of TA 2005, defined as increase from baseline in the forced expiratory volume over one second (FEV1), measured by spirometry, has been assessed in a preliminary clinical trial in a small group of asthmatic patients.

10 The results have shown that already following administration of a single dose of 1 μ g a mean and persistent increase of FEV1 approximately 30% greater than baseline can be obtained.

As said before, compound (A) is preferably used in the form of its hydrochloride salt (TA 2005). Other suitable physiological salts of compound (A) include bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, 15 benzoate, mesilate, ascorbate, salicylate, acetate, succinate, lactate, glutarate or gluconate. Solvates of salts such as hydrates, emihydrates or others with pharmaceutically acceptable organic solvents are also comprised in the invention.

20 Among the corticosteroids, acetal corticosteroids such as budesonide and its 22R-epimer, rofleponide and ciclesonide are particularly preferred. The medicament of the invention can comprise anticholinergic atropine-like derivatives such as ipratropium bromide, oxitropium bromide, tiotropium bromide or glycopyrrolate or its 3R,2'R-enantiomer, in order to provide a medicament particularly effective for the treatment of COPD.

25 The preferred anticholinergic, antimuscarinic agent is tiotropium bromide.

The ratios in which the compound (A) and a corticosteroid may be used in the combination of the invention are variable. Depending on the choice of

the steroid, the ratios by weight which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various steroids and their different potencies.

The pharmaceutical combinations according to the invention may
5 contain compound (A) and the corticosteroid in ratios by weight ranging from 1:3200 to 1: 10. In particular for budesonide and ciclesonide, the ratio by weights ranges from 1:1600 to 1:50, preferably from 1:1000 to 1:50.

Another corticosteroid that can be advantageously used in the combination is mometasone furoate and in this case the ratio by weights will
10 range from 1:800 to 1:50, preferably 1:400 to 1:100, more preferably 1:200 to 1:100.

For tiotropium bromide the ratio by weight ranges from 1:100, preferably from 1:50, more preferably from 1:20.

The intended dose regimen is twice or once daily, preferably once daily,
15 where the suitable daily dose of compound (A) is advantageously in the range of 0.5 to 8 µg, preferably of 1 to 4 µg, more preferably 1 to 2 µg or 2 to 4 µg, depending on the patient (age, weight and so on) and on the kind and the severity of the disease.

The combination of the invention is preferably administered by
20 inhalation. Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

For administration as a dry powder, single- or multi-dose inhalers known from the prior art may be utilized, wherein the powder can be filled in gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir.

25 A diluent or carrier, generally non-toxic and chemically inert to the medicaments, e.g. lactose or any other additive suitable for improving the respirable fraction can be added to the powdered medicament.

Inhalation aerosols containing propellant gas such as

hydrofluoroalkanes may contain the active ingredients of the combination of the invention either in solution or in dispersed form.

The propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

5 The propellant-free inhalable formulations comprising the combination of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art or by soft-mist nebulizers such as Respimat®.

10 Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic. Inflammatory or obstructive airways diseases to which the claimed combinations are applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma,
15 mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established
20 patient category of major medical concern. Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy.
25 Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g. between the hours of about 4 to 6 a.m., i.e. at a time normally

substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI),
5 adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD) including chronic bronchitis and emphysema, bronchiolitis, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy.

10 Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example,
15 aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tobacosis and byssinosis.

The invention further provides a pharmaceutical kit comprising compound (A) and at least a further compound (the combination compound), as hereinbefore described, in separate unit dosage forms, said forms being
20 suitable for administration of (A) and the combination compound in effective amounts. Such a kit suitably further comprises one or more inhalation devices for administration of (A) and the combination compound. For example, the kit may comprise one or more dry powder inhalation devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder
25 comprising a dosage unit of (A) and capsules containing a dry powder comprising a dosage unit of the combination compound. In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) and a multidose dry powder

inhalation device containing in the reservoir thereof a dry powder comprising the combination compound. In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising comprising (A) in a propellant and a metered dose inhaler containing an aerosol comprising the
5 combination compound in a propellant.

The invention is illustrated with reference to the examples which follow.

The unexpected features of the combination products of TA 2005 with a corticosteroid according to the present invention is demonstrated in an in vivo
10 model of Sephadex-induced lung inflammation according to the method reported by Kublin R et al Int Arch Allergy Immunol 1992; 98: 266-272; in an in vitro assay on human U-937 derived macrophage cell line as described in Naunyn-Schmiedeberg's Arch. Pharmacol., 362:184-189, 2000; as well as in a model of acetaldehyde induced bronchoconstriction (Berti et al., Arzneim-
15 Forsch/Drug Res 1994; 44: 323-326).

Moreover the pharmacological interaction between TA 2005 and the muscarinic M3-receptor antagonist, tiotropium bromide has been demonstrated in an in vitro and in vivo models.

Example 1 - In vitro assay on human U-937 derived macrophage cell line of the anti-inflammatory efficacy of the combination of the invention

U-937 cells were cultured and macrophage-differentiated by 10 ng/ml
25 phorbol myristate acetate for 48 h.

The cells were then incubated with 1 µg/ml lipopolysaccharide (LPS) or LPS together with concentration ranges of β_2 -agonist, corticosteroid, or combination. After different times of incubation TNF α and IL-10 were measured. Then the medium was collected and the cells lysed for cyclic
30 adenosine 3',5'-monophosphate (cAMP) measurement.

TNF α and IL-10 in the culture medium were determined by a commercial available ELISA assay, while cAMP was determined by a commercial ^3H -cAMP test system.

Dose-response curve of corticosteroid was determined in the absence
5 and in the presence of TA 2005 given at the concentrations of 10^{-10} and 10^{-8} M. Budesonide alone inhibited both TNF α and IL-10 release without affecting cAMP content. The addition of TA 2005 potentiated the effect on TNF α and counteracted the negative effect of budesonide on IL-10 release.

Interestingly the addition of TA 2005 resulted in a strong stimulation of
10 cAMP by budesonide.

Example 2 - In vivo assay of the anti-inflammatory efficacy of the combination of the invention in a Sephadex- induced lung oedema model

The rat lung oedema induced by Sephadex is a model which leads to inflammatory cells infiltration and long-lasting interstitial oedema. The
15 antiinflammatory activity of TA 2005 alone and in combination with budesonide in comparison with another long-lasting β_2 -adrenoceptor agonist, formoterol, was evaluated.

Anaesthetized rats (200-250 g) were dosed intratracheally with Sephadex beads (5 mg/ml) at a dose volume of 1 ml/kg. Control group
20 received 1 ml/kg saline.

The test substances were suspended in saline and administered intratracheally suitably diluted in the Sephadex suspension.

24 h post-administration, the animals were sacrificed and the lungs removed and weighted. Percent inhibition of the Sephadex-induced oedema
25 was then determined.

Intratracheal instillation of Sephadex beads induced a statistically significant increase in lung weight compared to control animals ($33 \pm 3\%$). Treatment with TA 2005 (0.001, 0.01, 0.05 and 0.1 nmol/kg), formoterol

(0.01, 0.1, 1 and 2 nmol/kg) and budesonide (15, 30, 60, 120, 240 and 480 nmol/kg) produced a dose-dependent remission of Sephadex-induced lung oedema. On the basis of the dose-response curves, non effective doses of TA 2005 (0.01 nmol/kg) and formoterol (0.1 nmol/kg) were chosen to be
5 combined with low, non effective doses of budesonide (15, 30, 60 and 120 nmol/kg). In the presence of TA 2005, budesonide was able to significantly inhibit the Sephadex-induced lung oedema already at a dose as low as 15 nmol/kg, while in its absence 240 nmol/kg was needed. In the presence of formoterol the potentiation was much less evident, as a significant
10 reduction in the Sephadex-induced lung weight increase was observed only with the 120 nmol/kg dose of corticosteroid.

Example 3 - Effects of TA 2005 and budesonide combination on the bronchoconstriction induced by acetaldehyde in the guinea pig

The ability of TA 2005 to control the bronchoconstriction and
15 neurogenic inflammation elicited by acetaldehyde (AcCHO) has been investigated in anaesthetized artificially ventilated guinea pigs, following the experimental model described by Berti et al., *Arzneim-Forsch/Drug Res* 1994; 44: 323-326.

Intravenous injection of AcCHO induced a dose-dependent
20 bronchoconstriction, accompanied by increase in blood histamine and Evans blue extravasation in the tracheal tissue, indicating alteration of vascular permeability.

The protective activity of TA 2005 (0.1 to 10 pmol), formoterol (0.3 to 30 pmol) or budesonide (31.25 to 500 nmol) was determined after
25 intratracheal superfusion alone or in combination.

All the effects of AcCHO were potently antagonised by TA 2005 and formoterol. However, TA 2005 was almost two fold as potent as formoterol in preventing bronchoconstriction, release of histamine and plasma

extravasation. TA 2005 displayed also a significantly longer duration of action at all doses selected. For example, when the two β_2 -adrenoceptor agonists were compared at almost equieffective doses as a peak (10 and 30 pmol), the anti-bronchoconstrictive effect of TA--2005 was still fully present after
5 240 min, whereas the effect of formoterol declined approximately by 50%.

The corticosteroid budesonide was also capable to lessen the effect of AcCHO in the guinea pig airways, but as expected, its efficacy was in the nanomolar range and noteworthy inferior to that observed with both TA 2005 and formoterol.

10 The tracheal superfusion of TA 2005 in combination with budesonide gave rise to a synergistic interaction in dominating the three main effects of AcCHO such as bronchoconstriction, histamine release and plasma extravasation in guinea pig airway. Considering the parameter bronchoconstriction, the ED_{50} value of budesonide alone (396 nmol) was
15 reduced 5.3 and 14.3 fold when it was combined with 0.1 and 0.3 pmol of TA 2005, respectively. A synergistic interaction was achieved also by adding formoterol to the corticosteroid. However, this combination was less effective than that obtained with TA 2005. In fact the ED_{50} value of budesonide was reduced 3.0 and 5.9 fold when it was combined with 0.3 and 1 pmol of
20 formoterol, respectively.

Example 4 - Effects of budesonide on the TA 2005-induced desensitisation in isolated tracheal strips from ovalbumin-sensitised guinea pigs

A prolonged use of β_2 -agonists results in down-regulation of pulmonary
25 β_2 -adenoceptors. This phenomenon can be counteracted by concomitant treatment with a corticosteroid.

In the present study tracheal strips obtained from ovalbumin-sensitised guinea-pigs (100 mg/kg ip and 100 mg/kg sc, 20 days before sacrifice) were

submitted to β_2 -desensitisation by contact for two 20-min periods with a supra-maximal concentration of salbutamol (5×10^{-6} M). In some experiments guinea pigs 24 and 1.5 h before sacrifice received 50 mg/kg ip of budesonide.

After β_2 -desensitisation, TA 2005 resulted about 3 times less potent in
5 relaxing the carbachol-induced contraction. Budesonide pretreatment reversed the rightward shift of the TA 2005 dose-response curves and even potentiated by about 6 times its relaxing effects.

Example 5 - Effects of TA 2005/tiotropium bromide combination on the carbachol-induced contraction in isolated guinea pig tracheal strips

10 The pharmacological interaction between the β_2 -adrenoceptor agonist TA 2005 and the M_3 -receptor antagonist tiotropium bromide was investigated in isolated guinea pig tracheal strips contracted with carbachol.

TA 2005 (10^{-12} M) and tiotropium bromide (3×10^{-10} M) inhibited the carbachol-induced contraction by $29.3 \pm 6.1\%$ and $17.1 \pm 2.2\%$, respectively.

15 When the two treatments were combined the relaxation was much greater ($59.1 \pm 7.7\%$).

The results are shown in the figure 1 (Note: CHF 4226 is synonymous of TA 2005).

**Example 6 - Effects of TA 2005 and tiotropium bromide
20 combination in the control of acetylcholine-induced bronchoconstriction in guinea-pigs**

Guinea pigs were prepared as originally described by Konzett and Rössler, Naunyn-Schmiedeberg's Arch Pharmacol, 1940; 195: 556-557.

Bronchoconstriction was induced by intravenous administration of
25 acetylcholine (20 μ g/kg). The antibronchospastic activity of different concentrations of tiotropium (0.1 to 30 pmol) or TA 2005 (0.3 to 100 pmol), alone or in combination, was investigated.

Both TA 2005 and tiotropium were able to dose-dependently antagonize

the acetylcholine-induced bronchoconstriction. Tiotropium resulted 5.2-fold ($P < 0.001$) more potent than TA 2005 ($ED_{50} = 3.2$ and 16.7 pmol, respectively).

When combined, a synergistic interaction was observed (figure 2).

- 5 The interaction was particularly evident when 0.1 pmol of tiotropium was combined with 3 pmol of TA 2005. In this instance, the effect of acetylcholine was reduced by 63% ($P < 0.001$), while in the absence of tiotropium the inhibition amounted to only 18% .

10 From the present results it is demonstrated that the M_3 -muscarinic receptor antagonist tiotropium and the β_2 -agonist TA 2005, superfused in combination onto the tracheal mucosa of anaesthetized guinea pigs, provide a synergistic interaction in limiting acetylcholine-induced bronchoconstriction.

Example 7 - Formulation for metered dose inhaler comprising TA 2005 and Budesonide

- 15 A HFA formulation for metered dose inhaler was prepared with the composition as follows:

<i>Components</i>	<i>Amounts</i>		
	Per unit		Nominal dose
	mg	%	μg
TA 2005	0.15	0.0016 w/v	1
Budesonide	30.00	0.317 w/v	200
Ethanol	1650.0	15 w/w	-
pH adjusted to about 3.5 - 4.0			-
Water (optional)	220.05	2.0 w/w	
HFA 134a q.s. to 9.45 ml	9114.5	-	-

The pH of the formulation has been adjusted with a suitable amount of a mineral acid.

- 20 The formulation (120 actuations/canister, overage of 30 actuations) was

filled in aluminum canisters having the internal surface coated with Teflon (two stage pressure filling) and fitted with a metering valve having a 63 μ l metering chamber.

Example 8 - Powder formulation for a dry powder inhaler
5 **comprising TA 2005 and Budesonide**

A powder formulation for dry powder inhaler was prepared with the composition as follows:

<i>Components</i>	<i>Amounts</i>	
	Per unit dose	
	mg	%
TA 2005	0.001	
Budesonide	0.400	
Alpha-lactose monohydrate 212-355 μ m	8.6151	86.2
Pre-blend	0.9839	10
Total weight	10	

Preparation of the formulation

10 The pre-blend mixture was obtained as follows: alpha-lactose monohydrate SpheroLac 100 (Meggles EP D30) with a starting particle size of 50 to 400 μ m and magnesium stearate with a starting particle size of 3 to 35 μ m in the ratio 98:2 w/w were co-milled in a jet mill apparatus.

About 86% w/w alpha-lactose monohydrate CapsuLac (212 - 355 μ m)
15 was placed in a 2.5 l stainless steel container, then about 10% w/w of the pre-blend mixture was added. The powder was mixed in a Turbula mixer for 4 h at 32 r.p.m. TA 2005 and budesonide were added to the powder and mixed in a Turbula mixer to obtain, respectively, a ratio of 1 μ g and 400 μ g of the active ingredients to 10 mg of carrier.

CLAIMS

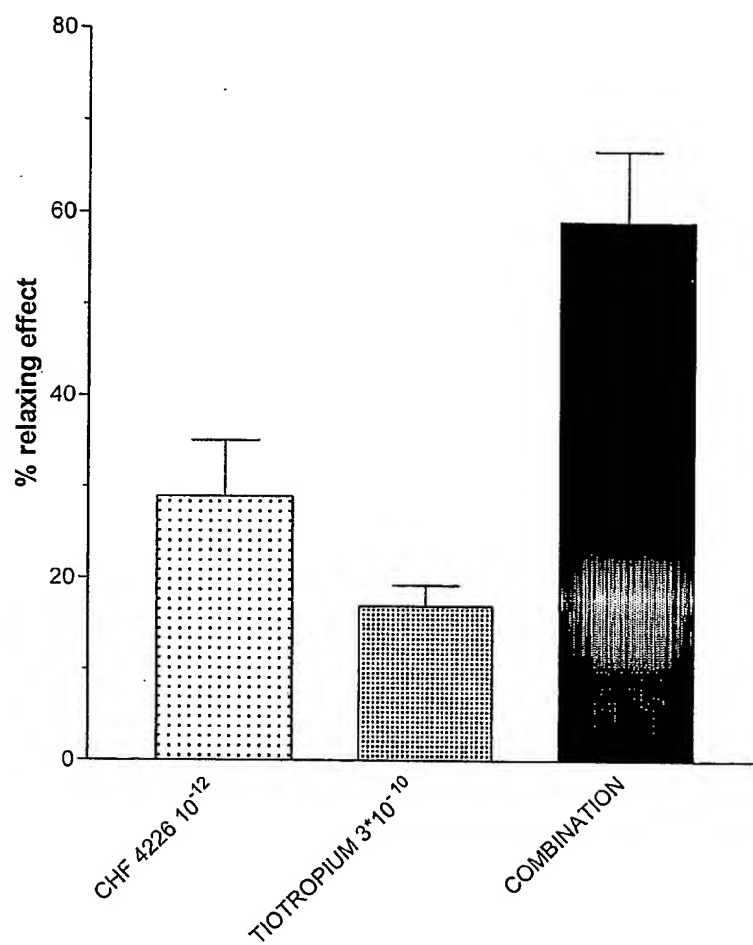
1. A combined preparation comprising:
 - 8-Hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl-2(1H)-quinolinone (compound A) and/or a
5 physiologically acceptable salt and/or solvate thereof
 - at least a further active ingredient useful for the treatment of the inflammatory or obstructive airways diseases, for simultaneous, sequential or separate use in the treatment of an inflammatory or obstructive airways disease, wherein the daily dose of the
10 compound (A) is the range of 0.5 to 8 µg.
2. A preparation according to claim 1 wherein the compound (A) is in the form of hydrochloride salt.
3. A preparation according to claims 1 and 2 wherein the daily dose is in
15 the range of 1 to 6 µg.
4. A preparation according to claim 3 wherein the daily dose is in the range of 1 to 2 µg.
5. A preparation according to claim 3 wherein the daily dose is in the range of 2 to 4 µg.
- 20 6. A preparation according to claims 1-5 wherein the further active ingredient comprises as corticosteroid, selected from budesonide and its epimers, beclometasone dipropionate, fluticasone propionate, flunisolide, ciclesonide, triamcinolone acetonide, rofleponide palmitate and mometasone furoate.
- 25 7. A preparation according to claim 6 wherein the corticosteroid is budesonide, the epimer 22R of budesonide, ciclesonide or rofleponide.
8. A preparation according to claim 5 wherein the ratio by weight between the compound (A) and the corticosteroid is from 1:3200 to 1:10.

9. A preparation according to claims 1-5 wherein the further active ingredient comprises an anticholinergic/antimuscarinic agent selected from the group of ipratropium bromide, oxitropium bromide, tiotropium bromide or glycopyrrolate.
- 5 10. A preparation according to claim 9 wherein the antimuscarinic is tiotropium bromide.
11. A preparation according to claims 1-5 wherein the further active ingredient comprises a phosphodiesterase-4-inhibitor.
12. A preparation according to claims 1-5 wherein the further active
10 ingredient comprises a corticosteroid and an antimuscarinic agent.
13. A preparation according to claims 1-5 wherein the further active ingredient comprises an antimuscarinic agent and a phosphodiesterase-4-inhibitor.
14. An inhalatory pharmaceutical composition comprising an effective
15 amount of the compound (A) and at least a further active ingredient, together with at least one pharmaceutically acceptable carrier.
15. A pharmaceutical composition according to claim 14 to be administered by pressurized metered dose inhalers wherein the active ingredients are in solution or suspension in a propellant gas.
- 20 16. A pharmaceutical composition according to claim 14 to be administered by a nebulizer comprising a solution or a suspension of the compound (A) and a corticosteroid in an aqueous, alcoholic or hydroalcoholic medium.
17. A pharmaceutical composition according to claim 14 to be administered by a dry powder inhaler in which the compound (A) and the further active
25 ingredient are in dry powder form.
18. A pharmaceutical kit comprising the compound (A) and at least a further active ingredient in separate unit dosage forms, said forms being suitable for administration of (A) and the further active ingredient in effective

amounts, together with one or more inhalation devices for administration of (A) and of the further active ingredient.

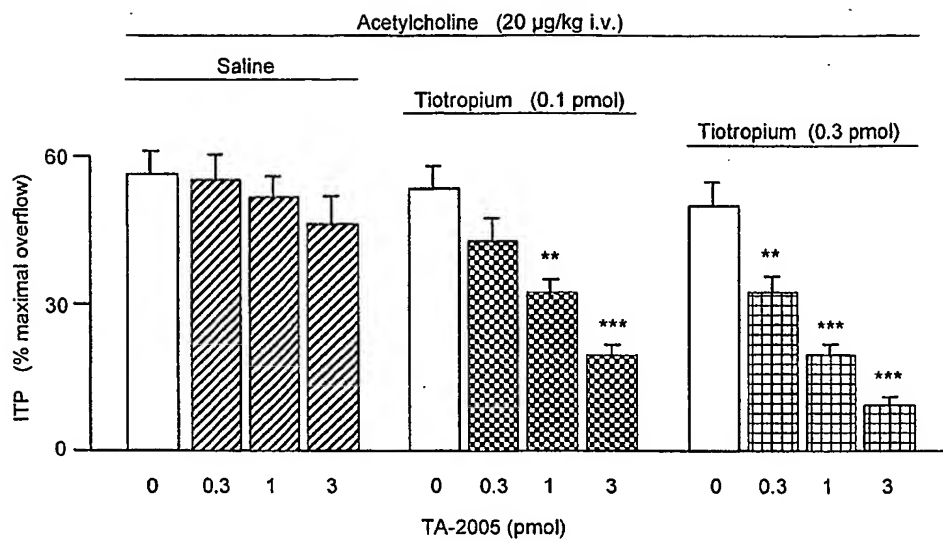
1/2

FIGURE 1



2/2

FIGURE 2



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP2004/001960

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/47 A61P11/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BIOSIS, EMBASE, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	[Online] XP002282993 Retrieved from the Internet: URL:www.chiesegroup.com/news/news-detail-e ng.asp?id=41> [retrieved on 2002-10-06] SEE PARAGRAPH 2, "Chiesi also plans to develop Ta 2005 in combination with a proprietary corticosteroid". 06/10/2002 -----	1-18
A	US 6 030 604 A (TROFAST JAN) 29 February 2000 (2000-02-29) column 1, lines 37-54 -----	1-18
A	WO 98/41193 A (SCHERING CORP) 24 September 1998 (1998-09-24) page 16, line 24 ----- -/--	1-18
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search 3 June 2004		Date of mailing of the international search report 05.08.2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Cattell, James

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001960

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 874 063 A (TROFAST EVA ET AL) 23 February 1999 (1999-02-23) column 2, line 34 -----	1-18
X	EP 1 157 689 A (CHIESI FARMA SPA) 28 November 2001 (2001-11-28) paragraph [0037] -----	1-18
X	WO 01/78693 A (BRAMBILLA GAETANO ; FERRARINI LORENZO (IT); VODDEN MORTON DAVID ALEXAN) 25 October 2001 (2001-10-25) claim 3 -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/001960

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 9-18(part)

TA 2005 with an anticholinergic/ antimuscarine agent

2. claims: 1-8(part) 14-18(part)

TA 2005 with a corticosteroid

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/001960

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6030604	A	29-02-2000	US 6287540 B1	11-09-2001
			AU 731192 B2	29-03-2001
			AU 5785998 A	07-08-1998
			BR 9811249 A	05-09-2000
			CA 2277913 A1	23-07-1998
			CZ 9902557 A3	13-10-1999
			EE 9900295 A	15-02-2000
			EP 1007017 A1	14-06-2000
			HU 0000714 A2	28-08-2000
			ID 21865 A	05-08-1999
			JP 2001508793 T	03-07-2001
			NO 993539 A	20-09-1999
			NZ 336594 A	26-01-2001
			PL 334527 A1	28-02-2000
			RU 2194497 C2	20-12-2002
			WO 9831352 A1	23-07-1998
			SK 95999 A3	18-01-2000
			TR 9901690 T2	21-09-1999
			TW 557217 B	11-10-2003
			ZA 9800078 A	20-07-1998
			US 5980949 A	09-11-1999
			US 5983956 A	16-11-1999
WO 9841193	A	24-09-1998	AU 741783 B2	06-12-2001
			AU 6537898 A	12-10-1998
			CA 2282360 A1	24-09-1998
			CN 1257423 T	21-06-2000
			EP 1393721 A1	03-03-2004
			EP 0969816 A1	12-01-2000
			HU 0002029 A2	28-11-2000
			ID 24472 A	20-07-2000
			JP 2000510478 T	15-08-2000
			NO 994519 A	19-11-1999
			NZ 337443 A	27-04-2001
			PL 335742 A1	08-05-2000
			SK 128099 A3	12-06-2000
			WO 9841193 A1	24-09-1998
			ZA 9802254 A	17-09-1998
US 5874063	A	23-02-1999	US 5637620 A	10-06-1997
			US 5562923 A	08-10-1996
			AT 137671 T	15-05-1996
			AT 208613 T	15-11-2001
			AU 662519 B2	07-09-1995
			AU 1534792 A	17-11-1992
			BG 61474 B1	30-09-1997
			BG 98147 A	15-11-1994
			CA 2106975 A1	12-10-1992
			CZ 9302116 A3	13-04-1994
			DE 69210601 D1	13-06-1996
			DE 69210601 T2	02-10-1996
			DE 69232207 D1	20-12-2001
			DE 69232207 T2	01-08-2002
			DK 580648 T3	16-09-1996
			DK 680752 T3	25-02-2002
			EE 2970 B1	15-04-1997
			EP 0508969 A1	14-10-1992
			EP 0580648 A1	02-02-1994

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/001960

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5874063	A	EP 0680752 A2	08-11-1995
		ES 2086733 T3	01-07-1996
		ES 2168322 T3	16-06-2002
		FI 934429 A	08-10-1993
		GR 3020602 T3	31-10-1996
		HK 52497 A	02-05-1997
		HU 65095 A2	28-04-1994
		IE 921144 A1	21-10-1992
		JP 3400999 B2	28-04-2003
		JP 6506454 T	21-07-1994
		JP 2003155228 A	27-05-2003
		KR 216384 B1	16-08-1999
		NO 933575 A	06-10-1993
		PL 168232 B1	31-01-1996
		PT 680752 T	31-05-2002
		RO 115779 B1	30-06-2000
		RU 2112507 C1	10-06-1998
		WO 9218110 A1	29-10-1992
		SG 43180 A1	17-10-1997
		SK 108893 A3	09-03-1994
		AT 199828 T	15-04-2001
		AU 681186 B2	21-08-1997
		AU 7626494 A	21-03-1995
		BR 9407320 A	16-04-1996
		CA 2170394 A1	02-03-1995
		CN 1133004 A ,B	09-10-1996
		CN 1195523 A ,B	14-10-1998
		CZ 9600544 A3	15-05-1996
		DE 69426934 D1	26-04-2001
		DE 69426934 T2	13-09-2001
		DK 717616 T3	11-06-2001
EP 1157689	A 28-11-2001	WO 0189480 A1	29-11-2001
		EP 1157689 A1	28-11-2001
		NO 20025568 A	20-11-2002
		AU 5070100 A	03-12-2001
		BG 107256 A	30-06-2003
		BR 0015884 A	08-07-2003
		CA 2411047 A1	29-11-2001
		CZ 20023835 A3	16-04-2003
		EE 200200649 A	15-06-2004
		HR 20021025 A2	29-02-2004
		HU 0302007 A2	29-09-2003
		JP 2003534266 T	18-11-2003
		SK 16522002 A3	01-04-2003
		US 2004047809 A1	11-03-2004
		US 2002025299 A1	28-02-2002
WO 0178693	A 25-10-2001	AU 4858101 A	30-10-2001
		AU 4859501 A	30-10-2001
		AU 4860101 A	30-10-2001
		AU 5834301 A	30-10-2001
		AU 6926101 A	08-01-2002
		BR 0110139 A	31-12-2002
		BR 0110141 A	28-01-2003
		BR 0110301 A	30-12-2003
		CA 2405767 A1	25-10-2001
		CA 2406119 A1	25-10-2001

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP2004/001960

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0178693	A	CA 2406201 A1	25-10-2001
		CA 2406206 A1	25-10-2001
		CA 2413692 A1	03-01-2002
		CN 1424909 T	18-06-2003
		CN 1438875 T	27-08-2003
		CZ 20023437 A3	12-02-2003
		EE 200200593 A	15-04-2004
		WO 0178693 A2	25-10-2001
		EP 1276472 A2	22-01-2003
		EP 1276473 A2	22-01-2003
		EP 1276474 A2	22-01-2003
		EP 1274406 A2	15-01-2003
		EP 1296651 A1	02-04-2003
		WO 0178694 A2	25-10-2001
		WO 0178695 A2	25-10-2001
		WO 0178696 A2	25-10-2001
		WO 0200197 A1	03-01-2002
		GB 2363987 A	16-01-2002
		GB 2363988 A	16-01-2002
		HU 0300490 A2	28-07-2003
		HU 0300499 A2	28-07-2003
		HU 0300593 A2	29-09-2003
		JP 2003530425 T	14-10-2003
		JP 2004500424 T	08-01-2004
		JP 2004501183 T	15-01-2004
		NO 20024971 A	17-12-2002
		NO 20024973 A	16-12-2002
		NO 20024980 A	17-12-2002
		NZ 521887 A	25-06-2004
		NZ 521972 A	25-06-2004
		SK 14912002 A3	04-03-2003
		US 2003180227 A1	25-09-2003
		US 2003175214 A1	18-09-2003
		US 2003162835 A1	28-08-2003
		ZA 200208066 A	05-08-2003
		US 2003185764 A1	02-10-2003